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INTRODUCTION

Variability in enzyme activities according to inherited polymorphisms could influence sensitivity of cells to cancer treatment. Glutathione S-transferase (GST) enzymes, particularly GSTA1 and GSTP1, catalyze inactivating glutathionyl conjugation reactions of chemotherapeutics including cyclophosphamide. The GSTA1*B variant reduces expression of GSTA1, while a GSTP1 Val¹⁰⁵, so these polymorphisms may improve treatment effect by reducing removal of the drug. We reported from a pilot study that among women treated for breast cancer, those who were homozygous for the GSTP1 Val¹⁰⁵ variant, which reduces specific activity toward alkylating agents, or homozygous for GSTA1*B, a promoter region variant that reduces hepatic expression of GSTA1, had longer overall survival than women with genotypes representing normal activity of these enzymes(1, 2). This topic continues to be an active area of research interest, as evidenced by data presented by other research groups at a 2003 national meeting(3, 4). The abstract that presented data on the association between GSTP1 and survival(4) described an association that was similar in direction in magnitude to what we had previously reported(1). In the present, DOD-funded study, we will conduct further research on the role of inherited variant alleles affecting activity of metabolizing enzymes and survival among breast cancer patients. We will consider whether these associations are independent of other prognostic markers in tumor tissue. The study uses a retrospective design, identifying women receiving first course of therapy for invasive, primary breast cancer, through a hospital tumor registry. Information on vital status and recurrence have been obtained from registry follow-up data. We will determine genotypes using DNA extracted from normal lymph node tissue available in archived surgical blocks. We will assess other prognostic markers in tumor tissue by

immunohistochemistry. We will use survival analysis methods, taking into account other prognostic factors, to evaluate associations between genotypes and recurrence and overall survival.

BODY

This study will use archived tissue and data to examine survival of women treated for breast cancer in relation to inherited polymorphisms of drug metabolizing enzymes.

The Statement of Work identified five tasks, as follows:

Task 1. Compilation of Data for Eligible Subjects, Months 1-3

Task 2. Archived Tissue Specimens Obtained, Months 4-24

Task 3. DNA Extraction and Genotyping, Months 6-30

Task 4. Immunohistochemistry, Months 6-30

Task 5. Data Analysis and Report Writing, Months 18-36

During the first year of funding, we completed Task 1, compilation of tumor registry data for eligible subjects, and completed the study start-up activities including: IRB review and approval; hiring study staff; creating data collection forms for pathology report abstraction and pathological review of each case for eligibility; establishing a database for entering abstracted, unidentified data and tracking specimen status; training study staff on data collection procedures. During year 2, we have proceeded with Task 2, collecting tissue samples. Accrual has proceeded more slowly than expected due to some unanticipated circumstances. We have learned that for a higher than expected proportion of potentially eligible subjects identified from the tumor registry, no archived tissue specimens are in fact available. This has resulted in a smaller then expected yield of

specimens in proportion to the number eligible subject identified and reviewed. Turnover of trained personnel has also caused delays in data collection. However, collection of specimens is ongoing and we expect to make faster progress during year 3 because staff who left have been replaced and new staff have been trained. Activities a. through f. specified under Task 2 are currently in progress including obtaining pathology slides and blocks, review of slides by the study pathologist, and abstracting information from pathology reports into the study database. Samples are being prepared to carry out laboratory assays, Tasks 3 and 4, during year 3.

KEY RESEARCH ACCOMPLISHMENTS

As described in the Statement of Work, data collection tasks will continue into year 3, so no reportable scientific results are available at the end of year 2. The PI presented a poster describing study methods and rationale at the "Era of Hope" Department of Defense Breast Cancer Research Program Meeting, Orlando, Florida, September 26-28, 2002.

REPORTABLE OUTCOMES

Abstract

Sweeney C, Gulbahce HE, Coles BF. Metabolizing enzyme polymorphisms and prognosis among women treated for breast cancer. "Era of Hope" Department of Defense Breast Cancer Research Program Meeting, Orlando, FL, September 26-28, 2002.

CONCLUSIONS

This study will use archived tissue and data to examine survival of women treated for breast cancer in relation to inherited polymorphisms of drug metabolizing enzymes. Data collection activities are proceeding. As described in the Statement of Work, data collection tasks will continue into year 3, so no reportable scientific results are available at the end of year 2.

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APPENDICES

N/A